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TYROSINE DERIVATIVES**RELATED APPLICATIONS**

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5/19/09 This is a continuation application claiming priority under 35 U.S.C. § 120 to U.S.
10 application Serial Number 10/198,328, filed July 16, 2002, ^{now abandoned} which is a continuation of application
U.S. Serial No. 09/669, 779, filed September 25, 2000, now U.S. Patent No. 6,469,047 B1, which
claims priority under 35 U.S.C. § 119 to U.S. provisional application Serial No.60/156,062, filed
September 24, 1999, the entire disclosures of which are hereby incorporated by reference.

BACKGROUND OF THE INVENTION

15 The integrins are $\alpha\beta$ heterodimeric cell surface receptors involved in numerous cellular
processes from cell adhesion to gene regulation. Hynes, R.O., Cell, 1992, 69:11-25; Hemler, M.E.,
Annu. Rev. Immunol., 1990, 8:365-368. Several integrins have been implicated in disease
processes and have generated widespread interest as potential targets for drug discovery. Sharar,
S.R. et al., Springer Semin. Immunopathol., 1995, 16:359-378. In the immune system integrins are
20 involved in leukocyte trafficking, adhesion and infiltration during inflammatory processes.
Nakajima, H. et al., J. Exp. Med., 1994, 179:1145-1154. Differential expression of integrins
regulates the adhesive properties of cells and different integrins are involved in different
inflammatory responses. Butcher, E.C. et al., Science, 1996, 272:60-66. The $\alpha 4$ integrins (i.e.
25 $\alpha 4 \beta 1$ and $\alpha 4 \beta 7$) are expressed primarily on monocytes, lymphocytes,
eosinophils, basophils, and macrophages but not on neutrophils. Elices, M.J. et al., Cell, 1990,
60:577-584. The primary ligands for $\alpha 4$ integrins are the endothelial surface proteins mucosal
addressin cell adhesion molecule (MAdCAM) and vascular cell adhesion molecule (VCAM) with
lower affinity. Makarewicz, R. et al., J. Biol. Chem., 1994, 269:4005-4011. The binding of the $\alpha 4 \beta 7$
or $\alpha 4 \beta 1$ to MAdCAM and/or VCAM expressed on high endothelial venules (HEVs) at sites of
30 inflammation results in firm adhesion of the leukocyte to the endothelium followed by
extravasation into the inflamed tissue. Chuluyan, H.E. et al., Springer Semin. Immunopathol.,
1995, 16:391-404. Monoclonal antibodies directed against $\alpha 4 \beta 1$, $\alpha 4 \beta 7$, MAdCAM or VCAM
have been shown to be effective modulators in animal models of chronic inflammatory diseases
such as asthma (Laberge, S. et al., Am. J. Respir. Crit. Care Med., 1995, 151:822-829),
35 rheumatoid arthritis (RA; Barbadillo, C. et al., Springer Semin. Immunopathol., 1995, 16:375-379),
colitis (Viney et al., J. Immunol., 1996, 157: 2488-2497) and inflammatory bowel diseases (IBD;